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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,189	09/21/2006	Alexei Shir	29770	5260

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,189	SHIR ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2010 and 24 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *96-99,107,108,110-113 and 115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *96-99,107,108,110-113 and 115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/2/09, 4/11/10, 5/27/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed September 24, 2009 and Applicant's Response filed March 26, 2010.

Claims 103-106, 109, and 114 have been canceled. New claim 115 is acknowledged. Claims 96, 97, and 108 have been amended.

Claims 96-99, 107, 108, 110-113, and 115 are pending in the instant application.

Claims 96-99, 107, 108, 110-113, and 115 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

Applicant's Response to the 1.105 request is acknowledged. The Examiner acknowledges that Citation No. 6 on the Information Disclosure Statement filed February 7, 2007 is U.S. Provisional Patent Application No. 60/426,876 filed November 18, 2002.

Information Disclosure Statement

Applicant's information disclosure statement filed June 2, 2009 is acknowledged. The submission filed June 2, 2009 is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Applicant's information disclosure statement filed April 22, 2010 is acknowledged. The submission filed April 11, 2010 is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Applicant's information disclosure statement filed May 27, 2010 is acknowledged. The submission filed May 27, 2010 is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed May 27, 2009, claim 114 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is moot** in view of Applicant's Amendment filed September 24, 2009 to cancel claim 14.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed May 27, 2009, claims 96-99 and 103-114 were rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/23050 (submitted on Applicant's Information Disclosure Statement filed February 7, 2007), in view of Yamazaki et al. (Journal of the National Cancer Institute, 1998 Vol. 90:581-587, of record), Farrell et al. (submitted on Applicant's Information Disclosure Statement filed

February 7, 2007), and Ogris et al. (Journal of Biological Chemistry, 2001 Vol. 276:47550-47555, of record). **This rejection is moot** against claims 103-106, 109, and 114 in view of Applicant's Amendment filed September 24, 2009 to cancel these claims. **This rejection is withdrawn** against claims 96-99, 107, 108, and 110-113 in view of Applicant's Amendment to the claims filed September 24, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to claim 96 to require a composition comprising a specific targeting moiety comprising epidermal growth factor (EGF), a specific nucleic acid carrier comprising polyethylenimine (PEI) and a double stranded RNA (dsRNA) for treating a malignant glioma.

Applicant's Amendment filed September 24, 2009 necessitated the new grounds of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 96-99, 107, 108, 110-113, and 115 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing malignant glioma cells over expressing EGF receptors (EGFR), the method comprising exposing the malignant glioma to a composition of matter comprising (i) a dsRNA molecule, (ii) a nucleic acid carrier comprising PEI; and (iii) a targeting moiety

comprising EGF, does not reasonably provide enablement for a method of killing any/all malignant glioma cells, the method comprising exposing the malignant glioma to a composition of matter comprising (i) a dsRNA molecule, (ii) a nucleic acid carrier comprising PEI; and (iii) a targeting moiety comprising EGF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The instant claims are drawn to a method of killing malignant glioma cells, the method comprising exposing the malignant glioma to a composition of matter comprising (i) a dsRNA molecule, (ii) a nucleic acid carrier comprising PEI; and (iii) a targeting moiety comprising EGF, wherein the dsRNA, targeting moiety and nucleic acid

carrier form a particle which penetrates tumor tissue, thereby killing the malignant glioma. The broadness of the methods recited in the claims implies *in vivo* applicability for enablement purposes. The nature of the invention, therefore, requires the knowledge of using dsRNA molecules to penetrate and kill malignant glioma cells in a subject.

The amount of direction or guidance and presence/absence of working examples:

Applicants have disclosed that malignant glioma cells over expressing EGF receptors are selectively killed using a composition comprising dsRNA which induces viral-like dsRNA mediated apoptosis, triggered by up-regulation of interferon (IFN)-α/β expression, a nucleic acid carrier (PEI), a targeting moiety (EGF), and melittin. See specification, throughout.

Similarly, the art has shown that EGF-targeted synthetic dsRNA is delivered selectively to malignant cells with an abnormally high number of EGF receptors and malignant tumors are killed. See Shir et al. (PLOS Medicine, 2006 Vol. 3:0125-0135).

Shir et al. also teach:

> "A major challenge in the treatment of GBM is to kill the accessible cancer cells on the surface of the tumor more rapidly than the rate of replication of the cells"; and

> "We would like to suggest that the strategy of ligand-guided delivery of dsRNA described here, can in principle, be applied to other cancers in which a particular receptor is over-expressed and undergoes endocytosis. Receptors that are over-expressed in many tumors and qualify as candidates for targeting poly(IC) include the transferrin receptor… the PDGF receptor… and the IGF-1 receptor"

Applicant's specification discloses, "Malignant gliomas are typically characterized by over expression of growth factors". See page 1. The claims have been amended to

require a composition comprising a specific targeting moiety comprising epidermal growth factor (EGF), a specific nucleic acid carrier comprising polyethylenimine (PEI) and a double stranded RNA (dsRNA) for treating a malignant glioma. Given the latter and the former, such a malignant glioma as recited in the claims must over express EGF receptor.

The state of the prior art and the predictability or unpredictability of the art:

The claimed invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

It is well known in the art that malignant gliomas are hard to treat. For example, Applicant's specification at pages 1-3 details the difficulty in treating malignant gliomas due to their density. Shir et al. also discuss that because of the localization of glioblastoma, high selectivity is needed to achieve treatment.

The level of skill in the art:

The relative skill of those in the art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

The quantity of experimentation necessary:

A review of the instant application finds adequate guidance for a method of killing malignant glioma cells over expressing EGF receptors (EGFR), the method comprising exposing the malignant glioma to a composition of matter comprising (i) a dsRNA molecule, (ii) a nucleic acid carrier comprising PEI; and (iii) a targeting moiety comprising EGF. Although, Applicants clearly recognize the potential of killing other

malignant glioma, Applicants only teach the how to kill malignant gliomas over expressing EGFR. No technical guidance or exemplary disclosure is provided regarding other malignant tumors expressing or over expression other growth factors. As the discussion above indicates, the specific treatment of malignant glioma is highly unpredictable and highly selective.

Thus, it is maintained that Applicants are enabled for a method of killing malignant glioma cells over expressing EGF receptors (EGFR), the method comprising exposing the malignant glioma to a composition of matter comprising (i) a dsRNA molecule, (ii) a nucleic acid carrier comprising PEI; and (iii) a targeting moiety comprising EGF.

Since the specification provides adequate guidance for a method of selectively killing malignant gliomas overexpressing EGFR, and since resolution of the various complications in regards to targeting and treating malignant glioblastoma is unpredictable, one of skill in the art would have been unable to practice the invention, commensurate in scope with the claims, without engaging in undue trial and error experimentation.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
July 5, 2010